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(54) Title: CALCIUM SULFATE HEMIHYDRATE COMPOSITION HAVING UTILITY IN THE PRESENCE OF BLOOD

(57) Abstract

Calcium sulfate hemihydrate can be combined with calcium sulfate dihydrate to provide a composition capable of hardening in the presence of blood. The dihydrate can be added to the hemihydrate as a separate ingredient or by forming it on the hemihydrate in situ during the manufacture of the hemihydrate. An organic or inorganic material such as calcium phosphate material, which may be either resorbable or nonresorbable by body fluids, can be mixed with the hemihydrate material prior to contacting it with a wetting agent. In a preferred method, the calcium sulfate hemihydrate composition containing the calcium sulfate dihydrate is contacted with a wetting agent to initiate the hardening reaction which proceeds for a brief period of time prior to any contact with blood or similar proteinaceous material.

* See back of page

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# CALCIUM SULFATE HEMIHYDRATE COMPOSITION HAVING UTILITY IN THE PRESENCE OF BLOOD

## FIELD OF THE INVENTION

This invention relates to calcium sulfate hemihydrate compositions having set and hardening characteristics in the presence of blood and/or other body fluids which are useful in bone implant procedures and bone repair or reconstruction. These compositions are particularly useful either neat or in combination with organic or inorganic materials, such as calcium phosphate materials which may be either resorbable or nonresorbable by body fluids, employed in dental or orthopedic procedures, wherein the compositions come into contact with blood or proteinaceous materials during the setting and hardening process.

## BACKGROUND OF THE INVENTION

U.S. Patent No. 4,619,655 discloses animal implants comprising a binder lattice or scaffold of calcium sulfate hemihydrate (plaster of Paris) and a non-bioresorbable calcium material such as hydroxylapatite or other calcium phosphate ceramic particles. The calcium sulfate hemihydrate is used to bind the hydroxylapatite or ceramic particles whereby the particles are more readily shaped and handled during the implantation procedure. It has been discovered that the calcium sulfate hemihydrate is not only effective as a binder for the ceramic particles, but after implantation, the hemihydrate material is resorbed by the body fluids and is replaced by fibrovascular tissue.

However, after it is placed in the body, the implant material containing the hemihydrate comes into contact with body fluids, e.g. blood, which contain proteinaceous material. This proteinaceous material can strongly retard or totally inhibit the setting of the calcium sulfate hemihydrate.

One of the inventors of the subject matter of U.S. Patent No. 4,619,655 has subsequently disclosed in a published paper that this set retardation problem can be overcome by the

addition to the hemihydrate of potassium sulfate, either mixed as a powder with the hemihydrate or predissolved in the mixing water. It has been reported that with sufficient potassium sulfate present, the calcium sulfate hemihydrate will set even when blood alone is used as the wetting agent. This published information discloses that hydroxylapatite/plaster of Paris mixtures can be set in blood or body fluids by using either 10% potassium sulfate or 16.7% sodium chloride as accelerators. There are two concerns when using these well-known accelerators. First, in high concentrations of potassium or sodium ions, the gypsum (calcium sulfate dihydrate) which is formed by the hydrolyzed hemihydrate may form crystals which are weaker than normal forms of rehydrated gypsum particularly in high concentrations of potassium ions. Second, it is believed that these higher than normal biologic concentrations of potassium or sodium ions in the body may be deleterious to human or animal health.

As disclosed in U.S. Patent No. 4,681,644, calcium sulfate hemihydrate (plaster of Paris) when mixed with water combines with some of the water to form calcium sulfate dihydrate which sets to a hard solid mass in about thirty (30) minutes. This patent also states that the most common accelerator used for reducing the setting time of calcium sulfate hemihydrate is calcium sulfate dihydrate that has been ground to a high degree of fineness. However, in most instances the accelerator is added to a calcium sulfate hemihydrate composition which also contains set retarders, whereby the composition is "set-stabilized". These set-stabilized plasters are formulated so that subsequent contact with either a retarding or accelerating medium will not have any material effect upon the setting time of the plaster.

## OBJECTS AND SUMMARY OF THE INVENTION

It is an object of this invention to provide a calcium sulfate hemihydrate composition having hardening and set characteristics in the presence of body fluids, particularly blood, which are useful in bone implant procedures and bone repair or reconstruction.

It is also an object of this invention to provide a calcium sulfate hemihydrate composition which contains a substantial amount of an inorganic material such as calcium phosphate ceramic which composition has a predetermined hardening characteristic in the presence of blood.

It is another object of this invention to provide a method for hardening calcium sulfate hemihydrate in the presence of blood wherein the hemihydrate is contacted with a wetting agent prior to any contact with blood or similar proteinaceous material.

It is a further objective of this invention to provide a calcium sulfate hemihydrate composition containing calcium sulfate dihydrate which will harden within five (5) to ten (10) minutes in the presence of blood or other proteinaceous materials.

It is a still further objective of this invention to provide a calcium sulfate hemihydrate composition containing calcium sulfate dihydrate which is useful as a resorbable bone cement in conjunction with a "cementless" arthroplasty procedure.

Other objects and advantages of this invention will become apparent from the detailed description which follows.

It has been discovered that calcium sulfate hemihydrate can be combined with calcium sulfate dihydrate (gypsum) to provide a composition capable of hardening at a rapid rate in the presence of blood or other proteinaceous material. The calcium sulfate dihydrate may be added to the hemihydrate in the form of fine particles which function as seed crystals, i.e. by increasing the available surface area of nucleating sites. The calcium sulfate dihydrate can be either a finely ground natural or snythetic gypsum such as terra alba or a hydrated plaster material, or it can be a specially treated, climate stabilized calcium sulfate dihydrate material. Alternatively, the calcium sulfate dihydrate can be formed in situ by purposeful incomplete calcination of a gypsum feed material or a partial rehydration of calcium sulfate hemihydrate prior to use, but using these procedures,

it may be more difficult to control the amount of the calcium sulfate dihydrate present in the hemihydrate composition.

When incorporating the finely ground calcium sulfate dihydrate (gypsum) material in the hemihydrate, it has been found that very small amounts of the gypsum are effective in providing a calcium sulfate hemihydrate composition which will harden in the presence of blood in less than ten (10) minutes. For example, one and a half percent (1.5%) by weight of a powdered terra alba accelerator was effective in a cementless prosthesis implantation, and amounts as low as about one-tenth of one percent (0.1%) by weight of solids have been effective when added as a separate, finely-ground ingredient. On the other hand, when the calcium sulfate dihydrate crystals are provided by incomplete calcination or partial rehydration, there is generally less calcium sulfate dihydrate surface area per unit weight and greater amounts of calcium sulfate dihydrate are generally required for rapid hardening of the calcium sulfate hemihydrate in the presence of blood or other proteinaceous material. In general, amounts ranging from about one-tenth of one percent (0.1%) to about five percent (5%) by weight are effective in providing a sufficiently hardened material in between five (5) to ten (10) minutes, though amounts outside this range may be effective. Furthermore, it is generally preferred that there be no retarder present in the calcium sulfate hemihydrate composition.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A composition consisting essentially of hydroxylapatite (HAP) and calcium sulfate hemihydrate (plaster) has been developed for use in medical and dental applications. The plaster functions as a binder for HAP particles, and when moistened with water or saline solution, the composition will ordinarily harden in approximately seven (7) to ten (10) minutes. However, when used in a surgical procedure, the composition frequently comes into contact with blood which substantially retards or totally inhibits the hardening and setting properties of the calcium sulfate hemihydrate. In

general, the HAP/plaster ratio may range from about 6:1 to about 1:10 with a range from about 2:1 to about 1:1 being preferred.

The terms "set" and "harden" are often used interchangeably, however, in the context of the present invention there is a distinction. Set is the chemical crystallization of calcium sulfate dihydrate (gypsum) from calcium sulfate hemihydrate in the presence of water and provides the ultimate strength of the hydrated material. Rate of set is the time derivative of the setting process. Hardening is a measure of compressive strength development in calcium sulfate hemihydrate, or a composite material containing calcium sulfate hemihydrate, as set occurs, and it is dependent upon the chemical crystallization process. A convenient measure of hardening is the Vicat set test, ASTM C-472, as modified for laboratory testing.

One of the objectives is to formulate a HAP/plaster composition which, when mixed with water or saline solution, has a working time (a dough-like or fluid state) of about two (2) to ten (10) minutes. In addition, it would be desirable for the composition to harden as measured by the Vicat set test in less than one hour when mixed with or in the presence of blood. In order to increase the hardening of the hemihydrate in blood, several additives were evaluated.

As previously noted, these evaluations confirmed that potassium sulfate is an effective additive in hardening calcium sulfate hemihydrate in the presence of blood. However, there is substantial concern that these higher than normal levels of potassium ion concentration may be deleterious in humans. In addition, if the ultimate strength of the implant is a factor to be considered, e.g. load-bearing joints or bones, the formation of syngenite crystals which may be caused by a high concentration of potassium ions provides a weaker matrix than gypsum crystals.

Aqueous sodium chloride solution (saline) is usually present in hospital operating rooms, and the use of saline solution as the wetting agent for the calcium sulfate hemihydrate did improve its hardening characteristics in the

presence of blood. In view of its availability and its beneficial effect on hardening, use of saline solution is recommended for wetting the calcium sulfate hemihydrate composition containing the calcium sulfate dihydrate additive.

In accordance with this invention, calcium sulfate dihydrate (gypsum) is the preferred additive for making certain that the calcium sulfate hemihydrate/hydroxylapatite composition will harden in the presence of blood. It provided acceptable hardening using either saline solution or deionized water as the wetting agent. Since gypsum is a form of calcium sulfate, there are no potentially deleterious chemicals being introduced into the body. Gypsum is commercially available in a form which has excellent shelf-life stability.

The following is a detailed description of the evaluation:

EXAMPLE 1

Hydroxylapatite/calcium sulfate hemihydrate compositions were prepared in a 65:35 ratio and were moistened with deionized water, saline solution or calcium hydroxide solution. Whenever saline solution was used as the wetting agent, it was 0.9% saline made by mixing 9 grams of sodium chloride per 1 liter of deionized water. The calcium hydroxide solution was a saturated solution made by dissolving 5 grams of calcium hydroxide in 1 liter of deionized water. After 24 hours, the solution was filtered to remove the undissolved calcium hydroxide. Each additive was dissolved in a pre-measured amount of the 0.9% saline solution for incorporation into the HAP/plaster composition, with the exception of the gypsum which was added directly to the composition. The following additive amounts were used:

| Additive | % by weight of Hemihydrate |
|---|---|
| Calcium Sulfate Dihydrate (Gypsum) | 0.2 |
| Potassium Sulfate | 0.85 |

A 45 minute time limit was chosen as an acceptable time for the calcium sulfate hemihydrate composition to harden in the presence of blood. The Vicat set test was used to determine hardening. Hardening time is the time after which a 300 gram Vicat needle per ASTM C-472 will not penetrate of its own weight to the bottom of the sample using 200 grams of material in a 6 ounce capacity cup. In this evaluation, a modified ASTM C-472 test was used. A 300 gram needle was used but only 8 grams of sample material was tested (having a total depth of about 1/2 to 3/4 inch) and set was considered complete when the needle no longer significantly penetrated the surface.

Dog blood was used as the blood source to which sodium heparin was added as an anti-coagulant. The following procedure was followed:

1) Tare a 20-ml disposable beaker on a balance and add 5.2 +/-0.01 grams of hydroxylapatite, after which 2.8 +/-0.01 grams of medical grade calcium sulfate hemihydrate is added.

2) The powder composition is mixed thoroughly using a metal stirring spatula.

3a) When using gypsum as the additive, tare a second 20 ml disposable beaker on the balance and add 0.0056 +/-0.0008 grams of gypsum to the beaker, after which it is carefully poured into the first beaker and mixed thoroughly with the HAP/plaster composition. A third 20 ml is tared on the balance to which 1.12 +/-0.01 grams of wetting agent (deionized water, 0.9% saline or calcium hydroxide solution) is added.

3b) When using potassium sulfate, tare a second 20 ml. disposable beaker on the balance, add the required amount of potassium sulfate based on the hemihydrate weight, re-tare the beaker and add the required amount of wetting agent (0.9% saline or calcium hydroxide solution).

4) Tare another 20 ml disposable beaker on the balance and add 0.51 +/-0.01 grams of heparinized dog blood thereto.

5) Add the HAP/plaster composition to the beaker containing the wetting agent and thoroughly mix for about 1 minute using the stirring spatula.

6) Tap the beaker against the table-top to obtain a smooth surface of material. Wait for about 1.75 minutes.

7) At 1 minute and 45 seconds, begin to loosen the HAP/plaster composition from the beaker, and at the 2 minute mark, add the composition to the beaker containing the heparinized dog blood.

8) Fold the HAP/plaster composition into the blood until a uniform consistency is achieved.

9) Tap the beaker on the table-top to give a smooth surface of material and thereafter do not disturb except to check for the Vicat set.

10) Watch for the loss of gloss. Begin checking for the Vicat set about 5-10 minutes after the loss of gloss occurs.

The results reported in the table below are represented by a "YES" or a "NO". A "YES" indicates that the HAP/plaster composition achieved hardening, as measured by the Vicat set test in an average time less than 45 minutes after combining the powder composition and the wetting agent. A "NO" indicates that more than 45 minutes was required to achieve hardening. The controls demonstrate that without an additive, the HAP/plaster composition does not harden within 45 minutes as measured by the Vicat set test.

TABLE 1

| Additive/Wetting Agent | 45 Min. Vicat Set |
|---|---|
| $K_2SO_4$/Saline | YES |
| $K_2SO_4/Ca(OH)_2$ | YES |
| $K_2SO_4/H_2O$ | YES |
| Gypsum/Saline | YES |
| Gypsum/$Ca(OH)_2$ | YES |
| Gypsum/$H_2O$ | YES |
| Controls | |
| $H_2O$ | NO |
| $Ca(OH)_2$ | NO |
| Saline | NO |

These results demonstrate that gypsum and potassium sulfate were effective in hardening the calcium sulfate hemihydrate composition in the presence of blood. However, the potassium sulfate is not recommended for use in human implantations because of possible deleterious effects and the possible formation of weaker crystalline forms in the presence of potassium ions.

Several factors complicate the interpretation of plaster hardening experiments when blood is present. There are various blood sources, human and animal, and the set retarding effect of each type is variable and unpredictable. Blood samples for in-vitro testing usually contain anti-coagulants which may also have a significant effect upon the rate of set. An important factor is the timing of the initial contact of the plaster with the blood. If the blood, either alone or pre-mixed with water, is added directly to the hemihydrate composition, the hardening and the rate of set are substantially slower than if the hemihydrate is pre-mixed with the wetting agent (water or saline solution) and allowed to react for a period of time prior to being contacted by the blood.

The following example illustrates a worst case situation where the blood was mixed with the wetting agent and was present at the initiation of the setting reaction:

EXAMPLE 2

Several calcium sulfate hemihydrate compositions were prepared using either medical grade calcium sulfate hemihydrate (MGCSH) or hemihydrates having either a low water demand (LWD), a moderate water demand (MWD), or a high water demand (HWD) as the hemihydrate source. The MGCSH had a 2-5% calcium sulfate dihydrate content due to either incomplete calcination or rehydration. The wetting agent was either deionized water, blood or a mixture thereof. Both human blood (H. BLOOD) and dog blood (D. BLOOD) were evaluated. The Vicat set test was again used to determine hardening using a 300 gram Vicat needle. The following results were achieved:

TABLE 2

| Hemihydrate + Wetting Agent | cc. of Wetting Agent per 100g. Hemihydrate | Vicat Set |
|---|---|---|
| MGCSH + H. BLOOD | 50 | Set Overnight |
| MGCSH + 1:1 H BLOOD:$H_2O$ | 38 | Set Overnight |
| MGCSH + H. BLOOD | 30 | 78 Minutes |
| MGCSH + H. BLOOD | 30 | 87 Minutes |
| MGCSH + D. BLOOD | 30 | 5 Hours |
| MWD + H. BLOOD | 35 | Did not set in 24 hrs. |
| HWD + H. BLOOD | 44.7 | Did not set in 24 hrs. |
| MGCSH + D. BLOOD | 30 | 5.5 Hours |
| LWD + D. BLOOD | 30 | Did not set in 24 hrs. |
| LWD + H. BLOOD | 30 | Did not set in 24 hrs. |
| LWD + H. BLOOD | 25 | Set Overnight |
| LWD + H. BLOOD | 20 | 5 Hours |

whereas all of the hemihydrate compositions required at least one hour for the Vicat set, it must be noted that this was a worst case scenario. Furthermore, the MGCSH containing from 2 to 5% calcium sulfate dihydrate yielded the best results.

EXAMPLE 3

Several additives were tested for their effect on hardening as measured by Vicat set time, using the 300 gram Vicat needle as in Example 2, when added to calcium sulfate hemihydrate compositions and hydroxylapatite/hemihydrate compositions. Additives evaluated in these tests included a sugar-treated calcium sulfate dihydrate referred to as HRA (see U.S. Patent No. 3,573,947 for its method of preparation) and potassium sulfate. These tests were also a worst case situation wherein the blood was present at the initial wetting of the hemihydrate composition. Some of the compositions were mixtures of hydroxylapatite and calcium sulfate hemihydrate. The liquid:solid ratio is reported as cubic centimeters of the blood/saline solution/water mix per 100 grams of the hemihydrate or hemihydrate/hydroxylapatite composition. The saline solution was 0.9% sodium chloride. The results were as follows:

| Hemihydrate g. | Hydroxylapatite g. | HRA mg. | $K_2SO_4$ mg. | Saline cc. | Blood cc. | Liquid/Solid cc/100g. | Vicat Set |
|---|---|---|---|---|---|---|---|
| 25 | | 25 | | 4.625 | 4.625 | 37 | 2.5 hrs. |
| 8.33 | 16.6 | 25 | | 4.6 | 4.6 | 37 | Did not set |
| 8.75 | 16.25 | 25 | | 2.5 | 2.5 | 20 | Did not set |
| 25 | | 25 | 25 | 4.625 | 4.625 | 37 | 97 min. |
| 8.75 | 16.25 | 25 | 25 | 2.5 | 2.5 | 20 | Did not set |
| 25 | | 25 | 25 | 2.5 | 2.5 | 20 | 48 min. |
| 24.5 | | 500 | | 4.6 | 4.6 | 37 | 44.5 min. |
| 24.75 | | 250 | | 4.6 | 4.6 | 37 | 52.5 min. |
| 8.6 | 15.9 | 250 | | 2.5 | 2.5 | 20 | Did not set |

These test results demonstrate the difficulty in achieving hardening when the blood is present at the initial contact between the hemihydrate composition and the wetting agent. The HRA additive (sugar-coated calcium sulfate dihydrate) was effective and did achieve a Vicat set in less than 45 minutes when the amount was increased to 500 mg.

In prosthesis implantations, a procedure has been developed wherein polymethyl methacrylate, also known as bone cement, is used to fill the bone cavity between the host bone and the prosthetic device. One of the problems encountered in this "cemented" procedure is that frequently the implanted device becomes loose due to failure of the bond at the bone/cement interface.

A cementless prosthesis procedure has been developed which employs a prosthetic device which has a porous surface and eliminates the use of the polymethyl methacrylate bone cement. The porous surface of the implant permits bone ingrowth into the device which fixes it in position in the host bone. However, there are often gaps between the prosthetic device and the host bone which can interfere with bone ingrowth and renders such ingrowth unpredictable.

In accordance with this invention, a calcium sulfate hemihydrate composition containing a calcium sulfate dihydrate additive is used to fill the gaps between the prosthetic device and the host bone. The calcium sulfate hemihydrate composition is bioresorbable and is resorbed over a period of weeks. It has been found that it is replaced by bone and promotes the ingrowth of bone into the porous surface of the prosthetic device. It functions as a resorbable bone cement.

It is important that the resorbable bone cement harden rapidly and with sufficient strength to fix the implant in the host bone. In performing the implant surgery, it is quite possible (if not probable) that the filler material will come into contact with blood during the period it is hardening, and therefore, it is essential that this material be capable of hardening in the presence of blood. Furthermore, it would be desirable if the resorbable bone cement had a hardening time (in the absence of blood) of 5-10 minutes, thereby providing working properties similar to polymethyl methacrylate.

EXAMPLE 4

Slurry compositions were prepared using a medical grade calcium sulfate hemihydrate (MGCSH). It is preferred that

the resorbable bone cement be in the form of a slurry which can be drawn into a syringe and applied by injection to the surface of the host bone. The surgeon specified a preference for a material having a hardening time of 5-10 minutes. Food and pharmaceutical grade terra alba was used as the source of calcium sulfate dihydrate, and it was thoroughly mixed into the calcium sulfate hemihydrate. The medical grade calcium sulfate hemihydrate contained no gypsum other than the terra alba. The medical grade hemihydrate, containing no additives, had a Vicat set (using a 300 g. needle) of 22.5 minutes when 100 g. was mixed with 37 cc. of deionized water. However, in this Example, 0.9% saline solution was used as the wetting agent. The following results were achieved:

TABLE 4

| Hemihydrate | Additive | cc. Saline/100g. Solid | Vicat Set (min.) |
|---|---|---|---|
| MGCSH | | 37 | 11.5 |
| MGCSH | 1% Terra Alba | 37 | 8.5 |
| MGCSH | 1.5% Terra Alba | 37 | 7.25 |
| MGCSH | 1.5% Terra Alba | 32 | 5.75 |

Medical grade calcium sulfate hemihydrate containing 1.5% by weight of terra alba was supplied to a surgeon who evaluated the hemihydrate composition as a resorbable bone cement in a model "cementless" prosthesis in 3 dogs. Instructions for use of the hemihydrate/Terra Alba composition were as follows:

(1) Add 16 cc. of 0.9% saline solution to a mixing cup.

(2) Add the hemihydrate/Terra Alba powder (50 grams) to the saline solution after sterilizing the powder using high energy ionizing radiation.

(3) Allow the powder to be wetted by the saline solution for 1 minute, then mix vigorously for 30 seconds with a spatula.

(4) Draw the wetted composition into a syringe and inject it into the prepared site in the host bone.

Non-weight bearing implants were implanted in both humeri of each dog. The implants were made of a solid core titanium

alloy rod with a titanium fiber metal porous surface. Polyethylene spacers were used to maintain a 3 mm. gap between the implant and the host bone.

The calcium sulfate hemihydrate material was injected into the drilled hole of the left humerus around the previously implanted rod, thus filling the gap between the implant and the host bone. The outermost polyethylene spacer was inserted and the incision was closed in the usual manner. The control was the opposite right humerus where a titanium rod was implanted without the calcium sulfate hemihydrate material injected between the rod and the host bone.

Four weeks after the implantations, specimens were examined histologically and compared. There was proliferative woven bone formation in the gap which had been treated with the calcium sulfate hemihydrate filler material, with bone bridging the gap around approximately 95% of the implant. The bone penetrated the metallic fiber all the way to the core of the rod. In contrast, the control implants retained significant gaps, with about 90% of the implant circumference remaining bone free.

Having fully described the objectives and nature of this invention, what is claimed is:

THE CLAIMS

1. A composition capable of hardening in blood within about 10 minutes as determined by failure of a 300 gram Vicat needle to significantly penetrate the surface of a small sample of the composition consisting essentially of calcium sulfate hemihydrate, from about 0.1% to about 5% by weight calcium sulfate dihydrate and having no set retarder present in the composition.

2. The composition of Claim 1 in which the calcium sulfate dihydrate material is a finely ground gypsum which is thoroughly mixed with the hemihydrate to form a homogeneous mixture.

3. The composition of Claim 1 in which the calcium sulfate dihydrate material is formed in situ on the hemihydrate by incomplete calcination at the time the hemihydrate is manufactured.

4. The composition of Claim 1 in which the calcium sulfate dihydrate material is formed in situ on the hemihydrate by a partial rehydration of the hemihydrate material after it is prepared by calcining.

5. The composition of Claim 1 which also contains a wetting agent selected from water, saline solution, calcium hydroxide solution, blood and mixtures thereof.

6. A composition capable of hardening in blood within about 45 minutes as determined by failure of a 300 gram Vicat needle to significantly penetrate the surface of a small sample of the composition consisting essentially of a material selected from organic and inorganic materials, calcium sulfate hemihydrate, from about 0.1% to about 5% calcium sulfate dihydrate based on the weight of the hemihydrate, having no set retarder present in the composition, and the ratio of the organic or inorganic material to the calcium sulfate hemihydrate ranges from about 6:1 to about 1:10.

7. The composition of Claim 6 in which the material is a resorbable or nonresorbable calcium phosphate material.

8. The composition of Claim 7 in which the calcium phosphate material is hydroxylapatite.

9. The composition of Claim 8 in which the calcium sulfate dihydrate material is a finely ground gypsum which

is thoroughly mixed with the hemihydrate and the hydroxyl-apatite to form a homogeneous mixture.

10. The composition of Claim 8 in which the calcium sulfate dihydrate material is formed in situ on the calcium sulfate hemihydrate by incomplete calcination at the time the hemihydrate is manufactured.

11. The composition of Claim 8 in which the calcium sulfate dihydrate material is formed in situ on the calcium sulfate hemihydrate by a partial rehydration of the hemihydrate material after it is prepared by calcining.

12. The composition of Claim 8 which also contains a wetting agent selected from water, saline solution, calcium hydroxide solution, blood and mixtures thereof.

13. A method for hardening calcium sulfate hemihydrate compositions in the presence of blood which comprises adding from about 0.1% to about 5% calcium sulfate dihydrate to the hemihydrate composition based on the weight of the calcium sulfate hemihydrate, contacting said hemihydrate composition with a wetting agent selected from water, calcium hydroxide solution and saline solution, initiating the hardening reaction and allowing it to proceed for a period of time prior to any contact with blood or similar proteinaceous material, and thereafter contacting the wetted and partially hardened hemihydrate composition with blood or similar proteinaceous material.

14. The method of Claim 13 in which the initial hardening reaction is allowed to proceed for at least about 1 minute.

15. The method of Claim 13 in which the initial hardening reaction is allowed to proceed for about 2 minutes.

16. The method of Claim 13 in which a material selected from organic and inorganic materials is mixed with the calcium sulfate hemihydrate prior to contacting the hemihydrate with the wetting agent.

17. The method of Claim 16 in which the organic or inorganic material is a calcium phosphate ceramic material.

18. The method of Claim 17 in which the calcium phosphate ceramic material is hydroxylapatite.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/03543

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C04B 11/00,11/28; A61K 35/14; A61F 2/28
U.S.Cl.: 106/772,774,775,776; 424/529, 426; 623/16

## II. FIELDS SEARCHED

Minimum Documentation Searched [4]

| Classification System | Classification Symbols |
|---|---|
| U.S. | 106/772,775,776 424/529,426 623/16 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

APS, CAS, BIOSIS

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

| Category * | Citation of Document, [16] with indication, where appropriate, of the relevant passages [17] | Relevant to Claim No. [18] |
|---|---|---|
| X<br>Y | US, A, 1,460,396 (WIGGIN), 03 July 1923, see the entire document. | 1-2,4-5<br>3, 6-18 |
| X<br>Y | US, A, 4,681,644 (DOZSA), 21 July 1987, see columns 1-2. | 1-2<br>3-18 |
| Y | US, A, 4,619,655 (HANKER et al.), 28 October 1986, see the entire document. | 6-18 |
| Y | CA, A, 841,074 (KUNTZE), 05 May 1970, see page 1. | 6-18 |
| Y | US, A, 2,331,515 (SULLIVAN), 12 October 1943, see column 2. | 6-18 |
| Y | Proceedings of the 44th Annual Meeting of the Electron Microscopy Society of America, 1986, San Francisco, Hanker et al., "Setting of Composite Hydroxylapatite/ Plaster Implants with Blood for Bone Reconstruction", pp. 328-329, see the entire document. | 6-18 |

* Special categories of cited documents: [15]

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## IV. CERTIFICATION

| Date of the Actual Completion of the International Search [2] | Date of Mailing of this International Search Report [2] |
|---|---|
| 04 September 1990 | 15OCT 1990 |
| International Searching Authority [1] | Signature of Authorized Officer [20] |
| ISA/US | Jean C. Witz |

Form PCT/ISA/210 (second sheet) (May 1986)